Asthma and the outcome of sickle cell disease

ABSTRACT

Introduction: Sickle cell disease (SCD) is one of the commonest monogenetic diseases. Worldwide, there are 300,000 infants with sickle cell disease (SCD) born every year. Affected patients can die prematurely in their fifth decade as they suffer multi-organ damage, including pulmonary complications.

Areas covered: This review describes the pathophysiology of SCD and its pulmonary complications and discusses the relationship between asthma and the outcomes of SCD. Patients with SCD and asthma, but importantly recurrent episodes of wheeze (which may not be due to asthma) have an increased risk of acute chest syndrome (ACS), painful crisis, stroke and all-cause mortality. In SCD, there is an increased pulmonary vascular volume, which is a response to their chronic anemia. Data from adult and paediatric cohorts show such haemodynamic changes result in airflow obstruction and hence wheezing.

Expert commentary: The wheezing and lung function abnormalities which occur in SCD patients can be due to asthma, but in others reflects the vascular airway interaction occurring because of chronic anaemia. It is important to differentiate whether a SCD patient is wheezing due to asthma or SCD per se as it will affect the choice of appropriate treatment.

Key words: acute chest syndrome, asthma, sickle cell disease, wheezing

1. INTRODUCTION

Sickle cell disease (SCD) is one of the commonest monogenetic diseases [1]. Worldwide, there are 300,000 infants with SCD born every year [2] and there are 200 million carriers of sickle cell trait. SCD was first described in 1910 by James Herrick when he observed "peculiar elongated and sickle-shaped red blood corpuscles" in blood films from an African-American patient presenting with severe anaemia [3]. In 1949, Linus Pauling *et al* described SCD as the first "molecular disease" when they detected distinct electrophoretic anomalies in sickle haemoglobin [4]. Nowadays, the majority of patients with SCD in developed countries can expect to survive to adulthood [5], but the median survival is only in the fifth decade and many suffer multi-organ damage, including pulmonary complications [6]. Recent years have seen an increasing recognition of the importance of SCD-related cardiopulmonary disease, but there remains uncertainty regarding the role of asthma in the pulmonary complications [7]. Indeed, it is now clear that there are distinct respiratory phenotypes in SCD patients [8]. Hence, in this review we will describe the pathophysiology of SCD and the pulmonary complications and then review the literature to determine the relationship between asthma and this globally important haematological condition.

1.1 The pathophysiology of sickle cell disease

SCD is an autosomal recessively inherited haemoglobinopathy, most commonly arising from a point mutation in the gene coding for the beta-globin chain whereby valine is substituted for glutamic acid at position six. This results in a haemoglobin molecule (HbS), with an altered net electric charge and a tendency to form polymers when the protein is in its T-conformation in the deoxy state. The resulting internal stress and deformation of the affected erythrocytes

alters their mechanical and rheological characteristics, with consequent cell damage, reduction in erythrocyte lifespan and chronic haemolysis [10]. Due to saturation of protective haemoglobin scavenger proteins, nitric oxide bioavailability is reduced and a state of nitric oxide resistance develops (Figure 1) [11, 12]. The overexpression of cell-cell and cell-vascular adhesion molecules coupled with reduced erythrocyte membrane deformability promotes the formation of cellular aggregates and cell-endothelial adhesion. This results in injury to the vascular endothelium (Figure 2) [13], microvascular occlusion and downstream tissue hypoxia with consequent release of inflammatory cytokines and creation of a chronic pro-inflammatory state [14]. The lung is particularly prone to damage from these processes due to the low oxygen tensions found in the pulmonary venous system and the adverse impact of altered cell rheology on erythrocyte transit time, which prolongs the duration of exposure to the polymerisation-promoting environment. Compound heterozygosity for HbS and a rarer haemoglobin variant, such as haemoglobin C, generally results in a milder phenotype, whilst co-inheritance of HbS with a mutation for beta-thalassemia, can produce a wide spectrum of clinical phenotypes [9].

1.2 The pulmonary complications of SCD

1.2.1 Acute chest syndrome and sickle chronic lung disease

Acute chest syndrome (ACS) is a major cause of morbidity being the second most common cause of hospital admission and can result in premature death [15]. ACS episodes may account for as many as 14-25% of sickle related deaths [16]. Patients with ACS have fever, chest pain, tachypnoea, cough, or wheezing, key to the diagnosis is radiological evidence of new pulmonary infiltrates [17]. The Cooperative Study of Sickle Cell disease reported a 29% incidence of ACS over a two-year period in a large cohort of subjects with HbSS disease

[17]. ACS episodes are associated with a deterioration of cardiac function and an increase in pulmonary vascular pressures. Those changes are associated with an increased risk of death, suggesting that at least a proportion of the mortality due to ACS may be due to the acute development, or exacerbation of pre-existing, pulmonary hypertension and cor pulmonale [18]. Dysfunction of the autonomic nervous system, as evidenced by a reduction in parasympathetic activity, appears to be more common in patients with a history of ACS, suggesting a neutrally-mediated component to ACS pathophysiology [19]. ACS episodes often occur in hospitalised adult patients with SCD where it is usually preceded by an acute vaso-occlusive pain crisis [15, 17]. An increased risk of ACS is associated with younger age, higher steady-state haemoglobin concentration, elevated steady-state leucocyte count, lower HbF concentration [20], a history of smoking or smoke exposure [21] and in children and young adults, a diagnosis of asthma [22, 23]. ACS episodes tend to be more severe in HbSS disease compared to other genotypes [20]. More than 50% of children with HbSS suffer at least one ACS episode in the first decade of life [16]. Lung function has been shown to deteriorate with increasing age in SCD children and the rate of decline to be greater in young children in whom ACS episodes are more common [24]. In one series, children under four years of age were at greatest risk of ACS episodes [25].

Adults with sickle cell disease can suffer from parenchymal lung disease and pulmonary vascular disease. This spectrum of abnormalities is commonly referred to as ‘sickle chronic lung disease’ (SCLD). In some cases, these processes may progress to restrictive lung disease and/or pulmonary hypertension. There is no curative treatment for SCLD, but ACS episodes are the most significant risk factor. Hence, prevention and optimisation of treatment of ACS episodes would improve the long-term outcome of SCD.

1.2.2 Pathogenesis of acute chest syndrome

The incidence of ACS episodes is commoner and the episodes more severe in those with HbSS than HbSC [26]. Whilst some early reports suggested that the ACS incidence was lower in patients with the Arab-Indian haplotype which is associated with a higher HbF level, recent data indicate incidence is similar to that observed in African haplotypes [27]. The risk for ACS is also increased by certain endothelin NO synthase gene polymorphisms [28].

In both adults and children, pulmonary infection is implicated in many cases of ACS. In a large cohort of patients in the USA, an infectious pathogen was isolated in 54% of admissions for ACS from a total of 671 episodes [15]. These were predominantly atypical bacteria and viruses; community acquired encapsulated bacteria were only found in a minority of cases (< 10% of ACS episodes). A total of twenty-seven different pathogens were identified of which *C. pneumoniae* was the most frequent, followed by *M. pneumoniae* and respiratory syncytial virus. Parvovirus was associated with severe reticulocytopenia [15]. Compared to patients who were infected with mycoplasma strains, patients with chlamydia infections were more likely to suffer a vaso-occlusive event during their hospital stay and had higher mean haemoglobin levels [15]. Seasonal influenza infection has also been linked to ACS [29, 30]. Infection may precipitate ACS due to an enhanced susceptibility to inflammatory provocation. In studies of transgenic mice expressing human HbS, SCD mice exhibited a heightened susceptibility to inflammatory provocation by lipopolysaccharide and bacterial endotoxin, resulting in lung injury at levels of endotoxin that had no adverse effect on wild-type mice [31, 32].

Fat emboli may also play a significant role in the pathogenesis of ACS. Severe vaso-occlusive pain crises, typically involving the proximal skeleton, result in bone marrow infarction and necrosis resulting in the release of fatty contents into the bloodstream. In the pulmonary vasculature severe lung inflammation, acute pulmonary hypertension and hypoxaemia are triggered by means of direct mechanical occlusion and inflammation [33-36]. Fat-laden alveolar macrophages obtained during bronchoscopy are diagnostic of pulmonary fat embolism. In the national ACS study cohort, fat embolism was diagnosed in 16% of ACS cases in adults and children [15]. Another study found that patients with ACS in whom lipid-laden macrophages were identified in induced sputum followed a more severe clinical course, with more severe extra-thoracic pain and a greater incidence of neurological symptoms compared to patients without evidence of fat embolus [35].

Episodes of ACS are frequently temporally related to infarcts of the ribcage [37]. Subsequent restriction of chest wall motion and alterations in breathing pattern due to the pain and discomfort result in atelectasis and hypoventilation which contribute to the development ACS [38-40]. A study of breathing patterns adopted by SCD patients with both thoracic and non-thoracic pain found that rapid shallow breathing is a feature of patients with thoracic bone pain [41]. In SCD children admitted to hospital with acute back and/or chest pain, incentive spirometry has been used to improve ventilation and significantly reduced the incidence of acute pulmonary complications during the period of admission [42]. The use of opiates for analgesia during painful crisis has also been linked to hypoventilation and development of ACS [43].

Asthma has been linked to an increased risk of ACS. In a retrospective review of 139 children with SCD, those with asthma had four times as many ACS episodes as the non-

asthmatics, they also had an increased length of hospitalisation [23]. In another retrospective study, amongst 96 children with SCD, those with asthma had a significantly greater frequency of ACS episodes [44]. A retrospective review of electronic medical records of a USA children's hospital highlighted that ACS episodes were more common in those with asthma [45]. Asthma is also associated with recurrent ACS episodes. In a study of 80 SCD children, asthma (80% versus 40%) and particularly atopic asthma (53% versus 12%), were more common in children who had suffered recurrent episodes of ACS than in those who had suffered a single or no episode [46]. In a subsequent study, Boyd *et al* found that children with SCD and asthma suffered twice as many ACS episodes as those without asthma (0.39 vs. 0.2 episodes per patient-year) and that the children with asthma developed their first ACS episode at a significantly younger age (2.4 versus. 4.6 years) [22]. Those results were consistent with a study highlighting that a greater number of the children who had an ACS episode compared to those who had not were taking anti-asthma medication. Importantly, the children with a history of ACS had been diagnosed as asthmatic at a median of 3.5 (range 0.5-7) years prior to their first ACS episode, suggesting that asthma may predispose children with SCD to subsequent ACS episodes [47]. Those results were similar to those obtained in a later retrospective analysis of 297 children with ACS which found that SCD children with a diagnosis of asthma had an increased rate of ACS (0.31 events per patient-year vs. 0.16 events per patient-year) compared to those who did not [48].

1.3 Asthma and SCD

A diagnosis of asthma may increase the risk of other complications. Patients with SCD and asthma or a history of recurrent episodes of wheeze have been reported to have a significantly increased risk of painful crisis [49, 50], stroke [44] and all-cause mortality [51, 52]. Indeed,

data from experimental models of asthma in SCD mice support an asthma-SCD synergy. Using sensitisation with ovalbumin to generate an experimental asthma in chimeric mice expressing human HbA or HbS and wild-type controls, [53], Nandedkar et al demonstrated significantly greater mortality, following the primary sensitisation dose, in the SCD mice compared to the controls (10% versus 0%, $p<0.01$) [53]. In both SCD and wild-type mice, sensitisation was associated with markers of asthma including blood eosinophilia, peribronchial and perivascular eosinophil infiltration, elevated serum IgE, and basement membrane thickening, some of which showed a dose-response pattern in both HbA and wild-type mice. In the SCD mice, however, the peak inflammatory response occurred at a low dose of ovalbumin and, following high-dose aero-sensitisation 30% of the SCD mice died compared to 4% and 0% mortality in the HbA and wild-type groups, respectively [53]. Those data suggest a role for both SCD and asthma-related lung inflammation and that the two pathologies interact to amplify the inflammatory response.

1.3.1 Is asthma increased in SCD?

Asthma may be more common in children with SCD than the general population [46, 54], but this is not a universal finding. Making the diagnosis of asthma in children with SCD can be difficult as common asthma symptoms, such as wheeze and shortness of breath, can also be seen in SCD. In Nigerian children, wheezing with or without a cold was much more common in those with SCD, almost ten times greater; the only variable associated with wheezing was SCD status [55]. Furthermore, in a longitudinal study, cough and wheeze events were temporarily associated with increased pain in individuals with SCD without asthma. The authors, however, acknowledge their sample size was small and not all asthma diagnoses may have been correctly classified [56]. Asthma is characterised by variable airflow obstruction and bronchial hyper-reactivity resulting from chronic inflammation [57]. The diagnosis is

made more reliably by evidence of reversible airflow obstruction, laboratory markers of atopy or inflammation and/or a family history of atopic or allergic disease, but in practice the diagnosis is often made on the basis of the clinical presentation alone [58]. Indeed, in the majority of studies of asthma in SCD, the diagnosis was made by medical records review [22, 23, 44] or current use of anti-asthma [22, 59] medication. When assessing BHR, it is important to note that some children may only respond to an exercise challenge and others only to a cold air challenge [60] and that bronchial challenge testing may precipitate a painful crisis. Whilst bronchial hyper-responsiveness (BHR) may be more prevalent in patients with SCD compared to the general population, it can be independent of an asthma diagnosis [46, 61, 62]. BHR is associated with both elevated serum IgE and lactate dehydrogenase (LDH) levels [63], suggesting a potential role for intravascular haemolysis in mediating reactive airways disease in SCD. Furthermore, Chaudry *et al* reported that airflow obstruction was present even in young children with SCD, but this was not associated with increased methacholine sensitivity or elevated exhaled nitric oxide [64], both key asthma biomarkers. In a subsequent study, steady state exhaled nitric oxide was not associated in SCD children with an asthma diagnosis, wheezing symptoms, lung function measures or prior sickle cell morbidity but was associated with markers of atopy and increased risk of future ACS episodes [65]. Those data suggest that mechanisms other than asthma may also mediate wheeze, in patients with SCD. The differentiation as to whether a SCD patient is wheezing die to asthma or SCD per se is important as it will affect the treatment used. Systemic corticosteroids are often used in the management of asthma exacerbations, but can cause an increase in painful crises and perhaps cerebrovascular accidents in SCD [66, 67]. Furthermore, in a historical review, SCD children with ACS episodes who received inhaled corticosteroids had no significant differences in outcomes, regardless of whether they had a

diagnosis of asthma [68]. If the wheezing is due to SCD per se then SCD therapies are indicated.

1.3.2 Potential mechanisms for reactive airways disease in SCD

A number of potential pathways for mediation of reactive airways disease in SCD have been identified, some of which are distinct from those seen in asthma and arise as a consequence of SCD per se. In murine models of SCD, the pro-inflammatory state present in SCD has been shown to prime the bronchial mucosal immune system for allergen-induced inflammation [69] with increased total lymphocytes, CD8+ T cells and interleukins in bronchoalveolar lavage fluid, as well as increased CD4+, CD8+ and regulatory T cells in lung tissue and hilar lymph nodes. One proposed mechanism for increased airway inflammation in SCD children is that haemolysis contributes to airway changes similar to those found in asthma. Haemolysis causes hydrolysis of membrane phospholipids into arachidonic acid, which leads to formation of leukotriene B4 which is also associated with eosinophilic asthma [70]. Elevated leukotriene levels have been found in SCD in both murine and human studies [70]. Placenta growth factor, which is elevated in SCD has been shown in a mouse study to exacerbate airway hyperresponsiveness and may link the leukotriene and Th2-mediated pathways in asthma [71]. Other studies have also proposed that the effect of haemolysis on nitric oxide may cause the airway changes seen in SCD. Nitric oxide bioavailability is reduced by haemolysis by two mechanisms. Firstly, it is consumed by the free haemoglobin which results from the haemolysis. Secondly, lysed erythrocytes release arginase, reducing the availability of arginine for synthesis of nitric oxide. This causes vasoconstriction, endothelial activation and proliferation [70, 72]. Exhaled nitric oxide, a marker of asthma and steroid response, is reduced in SCD patients

[72]. Comparison of SCD children with age- and ethnicity-matched controls demonstrated the former did not have elevated airway nitric oxide flux nor did the levels correlate with airways obstruction [73]. Elevated alveolar pulmonary NO production, however, significantly correlated with pulmonary blood flow in children with SCD, which may reflect increased shear stress due to the hyper-dynamic circulation [73]. Further differences in the pathogenesis of the inflammation seen in SCD and in asthma have been reported. In SCD patients, airway obstruction and hyper-responsiveness correlated with markers of haemolysis and IgE levels, but unlike in asthmatics, they did not with eosinophil count, skin prick test or exhaled nitric oxide [70]. Furthermore, murine models have shown increased IL-6 and MCP-1 in SCD, which are associated with monocyte activation but not with allergic asthma [70].

1.3.3 A non-inflammatory mechanism for airflow obstruction: a vascular-airway interaction

Children and adults with SCD have an increased pulmonary vascular volume, which is a response to their chronic anemia resulting in a raised cardiac output and increased vascular recruitment and distension [74-76]. Data from adult and paediatric cohorts suggest such haemodynamic changes drive a pulmonary vascular-airway interaction which mediates a non-inflammatory form of airflow obstruction in SCD [77, 78]. In a cohort of adults with HbSS disease, two measures of small-vessel size were derived from CT scans and were independently linked to reductions in FEV_1, VC and $FEF_{25/75}$ and to increased respiratory system resistance and RV:TLC [77]. Those results were consistent with those from a cohort of children, in whom pulmonary capillary blood volume was negatively correlated with FEV_1, VC and FEF_{25-75} and positively correlated with respiratory system resistance [78]. The negative relationship between measures of pulmonary vascular volume and VC, FEV_1 and $FEF_{25/75}$ and a positive relationship with RV, RV:TLC and respiratory system resistance suggest that the elevated pulmonary vascular volume was related to an obstructive defect.

Furthermore, measures of pulmonary vascular volume correlated with reduced haemoglobin concentration in both studies, suggesting that haemolysis and chronic anaemia was a key process in causing the pulmonary function abnormalities [77, 78]. In addition, a prospective three-dimensional echocardiography/Doppler study of 122 adults with SCD and 30 ethnicity matched healthy controls demonstrated that tricuspid valve regurgitation was rarely related to haemodynamically significant pulmonary hypertension, but rather elevated cardiac output, biventricular dilation and volume overload, likely related to the chronic anaemia [79]. In a subsequent study, increased pulmonary capillary blood volume and airways resistance were seen to occur immediately following blood transfusion in children with SCD. Those changes were accompanied by significant reductions in FEV_1, VC and FEF_{25-75} and the change in lung function correlated with the increase in pulmonary capillary blood volume [80]. Those results further support a vascular-airway interaction.

1.3.4 Therapies to improve lung function in SCD patients

Whilst randomised controlled trials of hydroxyurea incorporating pulmonary functions test outcomes are lacking, analyses of observational data suggest that hydroxyurea significantly attenuates the age-related decline in forced expiratory volume in one second and forced vital capacity in children with SCD [81]. Whether this reflects a reduction in ACS frequency or a direct effect of improved haematological characteristics on cardiopulmonary function, or a combination of the two is uncertain, but the resolution of these questions should form a key part of future efforts to develop SCD-specific treatments to reduce respiratory complications.

1.3.5 SCD-related respiratory disease in low- and middle-income countries

SCD is a global disease, and the greatest burden of SCD-related morbidity is borne by low- and middle-income countries (LMICs). Detailed phenotypic data from many of those

countries, especially those in sub-Saharan Africa and the Indian sub-continent, are sparse compared to Western Europe and the USA. Recent data, however, suggest that the prevalence of wheeze, airflow obstruction and ACS in some LMIC countries are broadly similar to that observed in high-income settings [46, 52, 55]. In contrast, a small study of 25 Malawian children reported a predominantly restrictive pattern, with no evidence of obstructive lung disease or increased prevalence of wheeze. The authors suggested that physiological evidence of airflow obstruction may be masked, in certain contexts, by the early onset of restrictive lung disease [83]. Interestingly, in a large study (n=8504) of Jamaican cohorts [84] significant independent associations were found between a history of "respiratory problems" (an aggregate term which included asthma and ACS) and climatic conditions, proximity to industrial activity and urban residence. Respiratory problems in SCD patients in LMIC settings thus may be modulated by complex interactions between disease status, industrial and economic development, and increasing urbanisation,

2. Conclusion

We have highlighted that asthma is associated with increased SCD complications, but a physician's diagnosis of asthma is inadequate to determine causation or appropriate treatment. Wheezing can occur due to SCD per se and wheezing in the absence of a diagnosis of asthma can increase SCD pulmonary complications. Importantly, lung function abnormalities and wheezing may occur from a vascular-airway interaction due to chronic anaemia which results in an increased pulmonary vascular volume. It is thus essential if a SCD child's treatment is to be optimised to determine by appropriate investigation if indeed they do have asthma. We suggest that pulmonary function testing, including measurement of lung volumes and bronchodilator responsiveness and skin-prick testing to assess atopy,

should form part of the routine assessment of patients with SCD, especially those with respiratory symptoms or a history of ACS.

3. Expert commentary

SCD is an important global health problem as the associated acute and chronic pulmonary complications cause a high burden of morbidity and early mortality. Asthma has long been associated with SCD-related complications, including acute chest syndrome, but in recent years there has been appreciation of the complexity of the relationship between asthma, SCD and pulmonary dysfunction. This has led to an awareness that current approaches to the diagnosis and management of asthma and wheezing in SCD patients are inadequate. Indeed, there are no appropriately designed studies to assess whether SCD therapies such as hydroxyurea or asthmatic preventions or treatments improve the long term outcomes of children with SCD. Furthermore, if the clinical management of children and adults with SCD is to be optimized, an improved understanding of the phenotypic complexity and the mechanistic basis of SCD-related cardiopulmonary disease will be required. Such an understanding will form the basis of new diagnostic approaches and the development of SCD-specific treatments. Given the degree of phenotypic diversity, SCD is a prime candidate for the development and implementation of a "stratified medicine" approach to treatment. This, however, will require a coordinated effort to integrate the efforts of basic, translational, statistical and computational researchers and clinicians within a strong collaborative framework, with data sharing and pooling of resources. A key component of such a programme will be the extension of research efforts from Europe and North America

to the low and middle income countries who bear the greatest burden of SCD-related morbidity. The development of such large-scale and integrated research efforts will present formidable challenges, but we can look to colleagues working in other parts of respiratory medicine for inspiration. The success achieved in understanding and treating the pulmonary and non-pulmonary complications of cystic fibrosis is of particular note and may provide a template for future efforts in SCD. The success in CF has recently been discussed [82] and includes capture of routine clinical and physiological data at scale by means of patient registries to identify risk factors for morbidity. The results have then been used to inform the development of rigorous mechanistic studies to elucidate disease-specific physiological, cellular and genetic pathways potentially amenable to pharmacological modification. The data has then been synthesised to develop evidence-based clinical guidelines and standardised protocols for diagnosis and treatment. We hope that similar efforts in SCD will yield equally impressive results. Assessment of wheezing, breathlessness and exercise intolerance should form a routine part of the assessment of parents with SCD and, where resources are available, pulmonary function testing should be conducted routinely Affected patients should be managed by a multidisciplinary team with input from a respiratory specialist (Figure).

4. Five-year view

In the coming years, we expect to see the development of large-scale patient registries to capture, on a routine basis, a wealth of clinical data on large cohorts of adults and children with SCD from Africa, the Caribbean, the Americas, Europe, the Middle East and the Indian sub-continent. Deep phenotyping will be key, including clinical outcomes and genetic, physiological and environmental data. Such data will facilitate the use of modern statistical, machine learning and systems biology approaches to identify new targets for specific SCD

pathologies and will form the basis of large-scale clinical trials of personalised medicine approaches to the treatment SCD-related lung disease.

5. Key issues

- Asthma has been associated with SCD and with an increased incidence and/or severity of complications.
- Recent work has demonstrated alternative inflammatory and non-inflammatory pathways, intrinsic to SCD, which may be responsible for some of the asthma-like symptoms in SCD. These include haemolysis-mediated lung inflammation and extrinsic airway compression due to increased pulmonary vascular volume.
- The existence of alternative mechanisms for airflow obstruction in SCD complicates making a diagnosis of asthma, but provides new targets for therapeutic intervention and prevention of SCD-related cardiopulmonary morbidity.
- New research strategies are required to understand the mechanistic basis of SCD-related airflow obstruction, to develop diagnostic tests for asthma in patients with SCD, and to optimise the clinical management of individuals with this debilitating disease.

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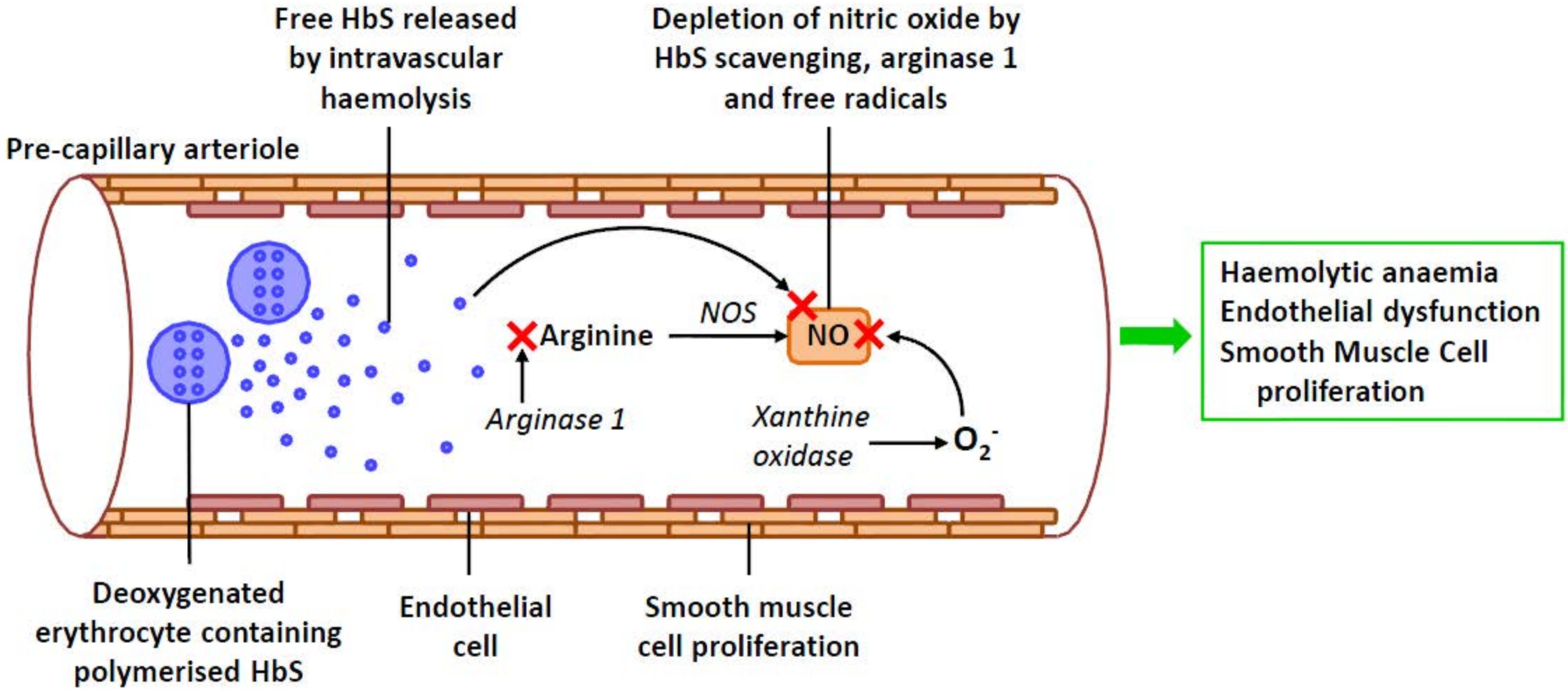
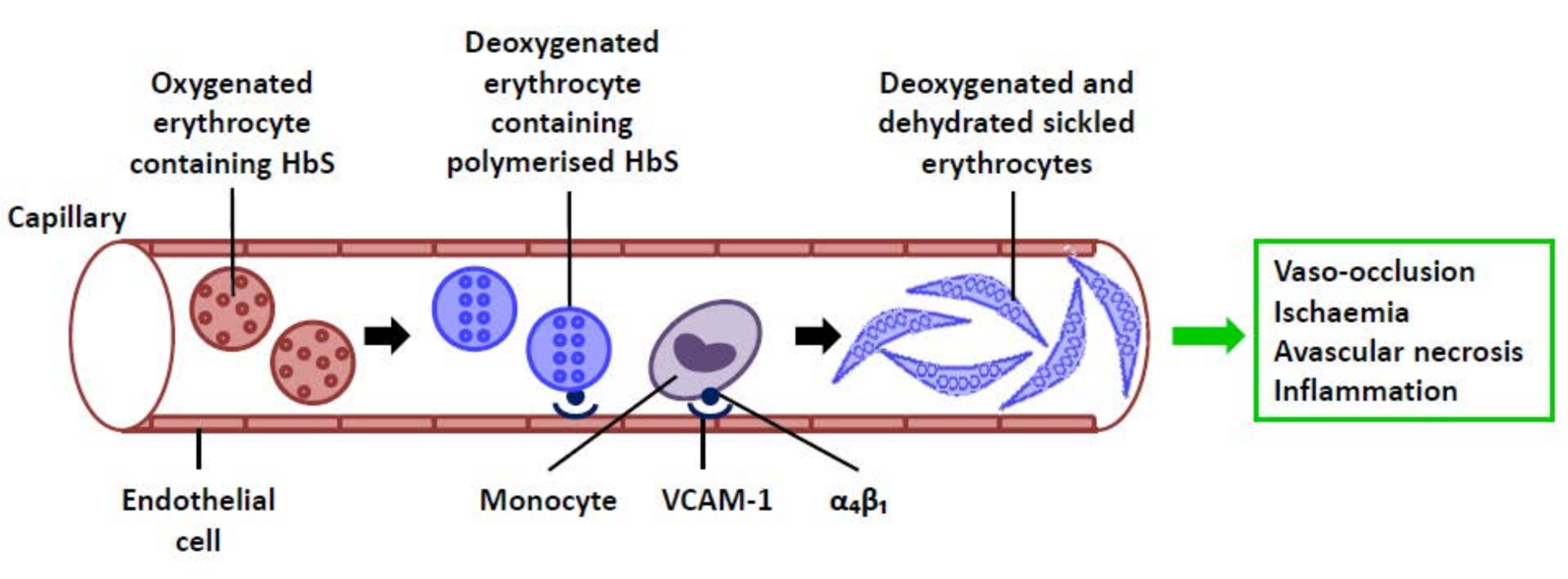
FIGURE LEGENDS

Figure 1: Vasculopathy in SCD. Polymerisation of HbS leads to reduced erythrocyte lifespan and increased intravascular haemolysis. Circulating nitric oxide (NO) levels are reduced due to scavenging by free HbS, free radical generation by xanthine oxidase, superoxide (O_2^-) and reduced bioavailability of substrates such as arginine (Arg) for nitric oxide synthase (NOS) due to arginase-1 mediated catabolism. These processes result in haemolytic anaemia and a chronic vasculopathy characterised by smooth muscle proliferation and endothelial dysregulation.

Figure 2: Vaso-occlusion in SCD. Deoxygenation of HbS-bearing erythrocytes causes HbS polymerisation and erythrocyte sickling. Leukocytes and polymerised erythrocytes form aggregates which adhere to endothelial cells via interaction of the $\alpha_4\beta_1$ molecule with vascular-cell adhesion molecule-1 (VCAM-1), a process which is promoted by increased VCAM-1 expression arising from the inflammatory milieu present in persons with SCD. This process results in microvascular occlusion and vaso-occlusive pain crises, including ACS.

Figure 3: Algorithm to investigate wheezing child with SCD


Free HbS released by intravascular haemolysis
Depletion of nitric oxide by HbS scavenging, arginase 1 and free radicals
Pre-capillary arteriole
NOS
Arginine
NO
Arginase 1
Xanthine oxidase
O_2^-
Haemolytic anaemia
Endothelial dysfunction
Smooth Muscle Cell proliferation
Deoxygenated erythrocyte containing polymerised HbS
Endothelial cell
Smooth muscle cell proliferation


Oxygenated erythrocyte containing HbS
Deoxygenated erythrocyte containing polymerised HbS
Deoxygenated and dehydrated sickled erythrocytes
Capillary
Endothelial cell
Monocyte
VCAM-1
α4β1
Vaso-occlusion
Ischaemia
Avascular necrosis
Inflammation

SCD child with wheezing

Suspect asthma if:

- Parental history of asthma
- Two positive allergen skin tests
- Child over four years of age
- ACS episodes without chest x-ray changes

Lung function testing showing obstructive abnormalities

Positive response to bronchodilator

If significant wheezing
bronchodilator & inhaled steroids

No response to bronchodilator

Investigate pulmonary
capillary blood volume